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EFFECT OF DIFFERENT DOSES OF IVERMECTIN ON BIOMARKER HORMONE OF ADRENAL GLAND AND HISTOLOGY OF IT IN LOCAL FEMALE RABBITS

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Abstract

Ivermectin (IVM) is a lipophilic anthelmintic drug widely used for the control of internal and external parasites in both human and veterinary medicin. This study aimed to investigate the effect of different dose of Ivermectin (IVM) on the Cortisol hormones (functionally and histologically) of twenty four of mature female rabbits in basrah. Animals were randomly divided into four groups (six for each). The first group was left without treatment (control group), second, third and fourth group treated weekly by injection s/c ivermectin for 8 week at dose (0.5mg, 1mg and 2 mg / kg.bw) respectly .Results conducted to increase significant in cortisol concentration in fourth group ,while the first and second and third group did not affected when compared with fourth group or within them .The histopathological changes as a results of ivermectin treatment in adrenal there is representive by vacuolation of zona glomerulosa and zona fasculata in group fourth and less effect in other treatment. We concluded high dose of ivermectin and prolong period may affected on adrenal gland function.

Keywords: Ivermectin, Cortisol, Adrenal Tissue, Female Rabbits.

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Introduction

Ivermectin (IVM) is an anthelmintic drug widely used to control both internal and external parasites in humans and animals **(Makhlouf *et al.*, 2020**) IVM is a widely used FDA-approved broad-spectrum antiparasitic drug used also to treat pest insects and was found to be especially effective to decrease P. vivax transmission (Hotson 2020). However, IVM exhibits a broad spectrum of activity against gastrointestinal and lung nematodes as well as against ectoparasites of clinical relevance in domestic animals (Suarez *et al.*, 2013).

Additionally, there are different gaps regard European Food Safety Authority (EFSA 2016) ding mammalian endocrinal toxicology which are not properly addressed]. Several study investigation the effect of ivermectin histologically on different tissues Mahmoud et al.(2017) reported different doses of ivermectin induced pathological changes in hepatic tissue of female rabbits as vacuolation of hepatocytes and fibrosis. The severity of lesion depending on dose of administration. as well as, therapeutic and double therapeutic doses of ivermectin in male rats revealed significant decrease in total sperm count and mortality in addition to various pathological changes in liver, kidneys and testis including congestion of blood vessels also degenerative changes as vacuolar and hydropic degeneration or even necrosis were also observed and this pathological changes were associated with significant changes in liver and kidney functions (Elzoghby *et al.*, 2015).

Literature reviews: Ivermectin (fig. 1) overdose could cause a combination of clinical side effects ranging from mild to extremely severe (Epstein and Hollingsworth, 2013). The most dominant clinical symptoms of IVM poisoning in domestic and wild animals are CNS depression and sometimes coma, frequently resulting in death (Trailovic and Nedeljkovic, 2011). So, the use of ivermectin must be done with caution (Hutchinson *et al.*, 2009).

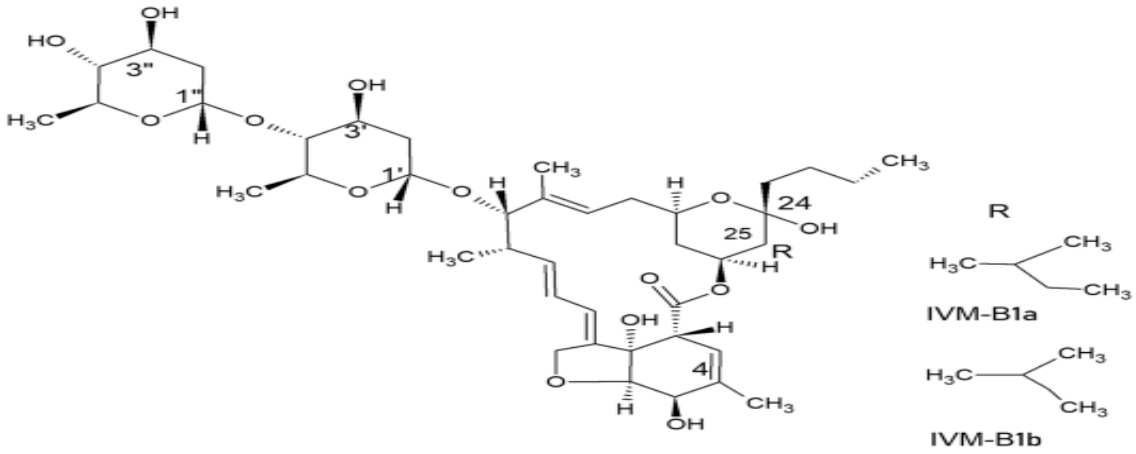

Fig. (1): Ivermectin B1a (IVMB1a) and B1b (IVM-B1b) (Archives of Toxicology)

The anticancer and the antiviral activity of IVM are well known. Thus recently, ivermectin was found to have an anti-cancer effect on human colon cancer and lung carcinoma (Diao *et al.*, 2019). Given the widespread of COVID-19 pandemic caused by Coronavirus 2 (SARS-CoV-2), researchers are constantly striving to find a suitable drug to treat this malady. (Gonçalves *et al.*, 2020) has concluded from the review of many realized works that IVM can inhibit the viral replication of SARS-CoV-2 (fig. 2).

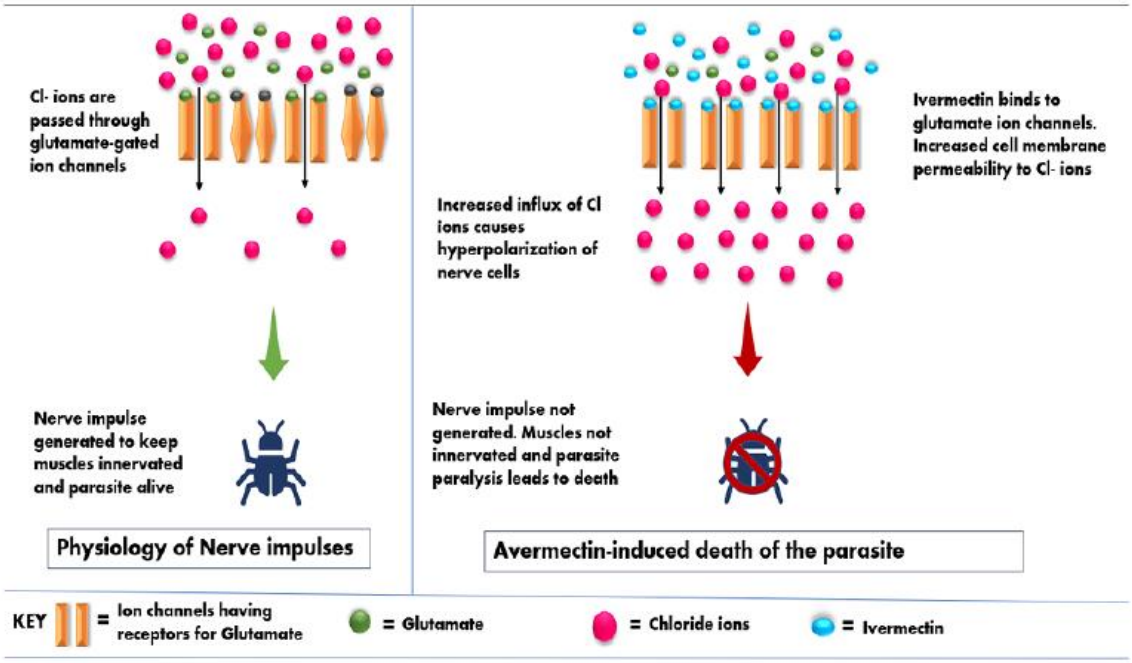
Cl- ions are passed through glutamate-gated ion channels
Nerve impulse generated to keep muscles innervated and parasite alive
Physiology of Nerve impulses
Increased influx of Cl ions causes hyperpolarization of nerve cells
Ivermectin binds to glutamate ion channels. Increased cell membrane permeability to Cl- ions
Nerve impulse not generated. Muscles not innervated and parasite paralysis leads to death
Avermectin-induced death of the parasite
KEY
= Ion channels having receptors for Glutamate
= Glutamate
= Chloride ions
= Ivermectin

Fig. (2): Mode of action of ivermectin (Muhammed *et al.*, 2022)

Commercially as an antiparasitic agent in both veterinary medicine and human (Burkhart, 2000). Ivermectin acts to enhance the release of GABA at presynaptic neuron. It act as an inhibitory neurotransmitter and block the post synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber in arthropods by stimulating the release of GABA and caused paralysis of the parasite and eventual death (Plumb, 2008; Yovany *et al.*, 2010). These harmful effects arise from avermectins targeting GABA and glutamate-gated chloride channels present both in the parasites and the host animals Muhammed et al.,(2022) for this reason the world health organization was listed ivermectin as most important essential medicine needed in a basic health system (WHO, 2013).

Various studies have indicated the ivermectin to have toxic effects on animals (Yas-Natan *et al.*, 2003 and Guizelin *et al.*,2020). Hopper *et al.* (2002) recorded a case of collie dogs experiencing severe illness presented to the clinic were found to be suffering from ivermectin to toxicity. Other studies conducted on cows indicated therapeutic doses of ivermectinto to induce hormonal changes, ultimately affecting the reproductive cycle of cows (Sadek and Shaheen 2015). Other studies have also revealed the administration of ivermectin even at therapeutic doses to cause reproductive, hepato-renal, sexual, and behavioural abnormalities in animals [Parisi, 2019; Nicolas *et al.,* 2020 and Ahmed *et al.*, 2020). At present, there is limited research available describing the role of ivermectin as endocrine disruptors.

AIM OF STUDY: Study the effects of different doses of ivermectin on cortisol hormone and histological study of adrenal gland in non-infected mature female rabbits.

Materials and Methods

Rabbits Housing and Management: This study done on 24 Healthy mature female rabbit (*Lepus cuniculus*) weighed 1250-1800 grams body weight from Basrah market. All rabbit were kept for two week in the animal house of the College of Veterinary Medicine / University of Basrah, for acclimatization. They were maintained on unrestricted supplies of food that consist of alfa alfa, concentrated pellets and water *ad libitum*.

Experimental Design: Twenty four healthy non pregnant female domestic rabbits were divided into 4 groups(6 rabbits/group).The first group treated S/c 0.9 % normal saline which

considered as a control ,while the second , third and fourth group were treated with (0.5 mg, 1mg and 2mg /kg .BW.) ivermectin respectly. The treatment were given S/c and weekly for 8 week, in the end of the experiment. blood samples were collected from the heart then was put in test tube without anticoagulant, centrfugated to collect serum and kept in ependrof tubes and stored at -20°C, for hormonal analysis.

Histological study: After sacrificed by all animals, harvested adrenals gland and kept in10% formalin for histological examination so, dehydration was done by passing in ascending concentration of ethanol; the glands were infiltrated by xylene and then embedded in paraffin wax. The section of embedded adrenal glands were done (5micron thick) by using microtome and after that put on glass slides that applied with by albumin mayer for fixed the section of gland ,dehydrated at hot plate overnight and finally staining by hematoxylin –eosin stain to examined by light microscope (Luna, 1968).

Results

Effect of different dose of ivermectin on cortisol hormone level in female rabbit: According to the results is table, there is no significant differences between group2 and group 3 which administrated with ivermectin when compared with control or with group 4. Whereas group 4 has a high dose of administration of ivermectin (2mg/kg.bw) causes a increase significant difference ($p< 0.05$) compared with group 2 (0.5 mg/kg bw) and group 3(1 mg/kg.bw) and with control group. just high dose of ivermectin that injection S/C caused increased significantly.

Table 1- Effect of different dose of ivermectin on cortisol hormone level in female rabbit (means±SE)

GROUP	CORTISOL LEVELS
G1 CONTROL	4.34±3.15 b
G2 (0.5 mg IVM)	4.80±3.07 b
G3 (1mg IVM)	7.90±1.93 b
G4 (2mg IVM)	13.46±3.36 a
LSD	9.123

Different letters denote significant differences ($p< 0.05$) between groups

Histological changes on adrenal gland: Section of adrenal gland of female rabbit figure (1) as control shows normal structure of adrenal cortex (zona glomerulus and zona faseculata). Figure (2): adrenal gland of female rabbit injection (0.5gm/kg.bw)s/c weekly for 8 week. Show vaculation of zona glomerulta and minimum vaculation of zona faseculata. Figure (3) adrenal gland of female rabbit injection (1gm/kg.bw) s/c weekly for 8 week. Show moderated vacuolation of zona glomerulosa. Figure (4) adrenal gland of female rabbit injection (2gm/kg bw) s/c weekly for 8 week. Show severs vacuolation of zona glomerulta and vaculation of zona faseculata.

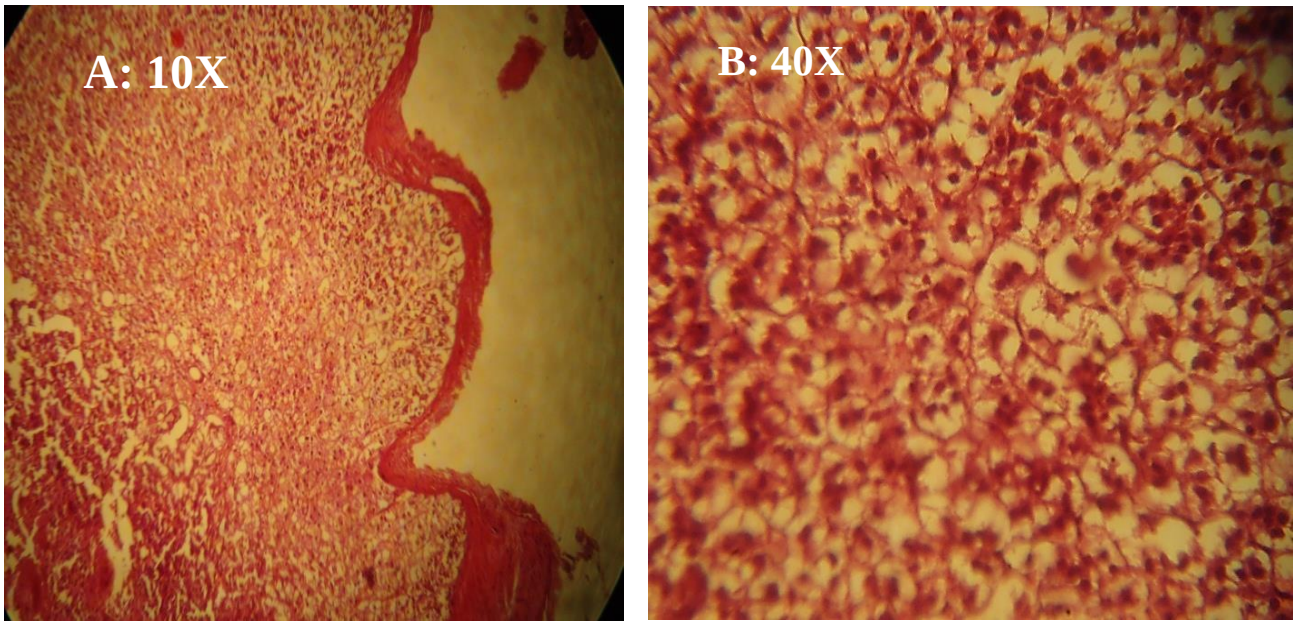

Figure (1): (control) Adrenal gland of female rabbit injection (1gm/kg.bw.) Ivermectin weekly for 8 weeks showed normal architecture. Eosin –hematoxylin stain (A: 10X and B: 40X)

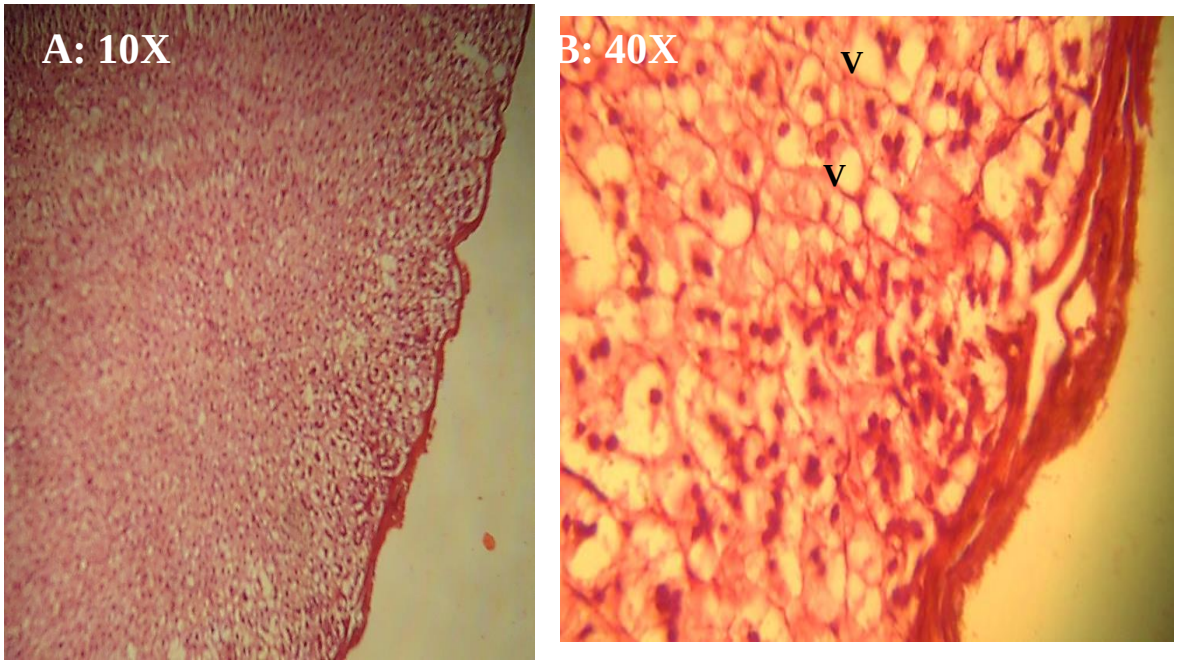

Figure (2): adrenal gland of female rabbit injection (0.5gm/kg.bw)s/c weekly for 8 week. Show vacuolation (V) of zona glomerulase and minimum vacuolation of zona faseculata. Eosin –hematoxylin stain (A: 10X and B: 40X).

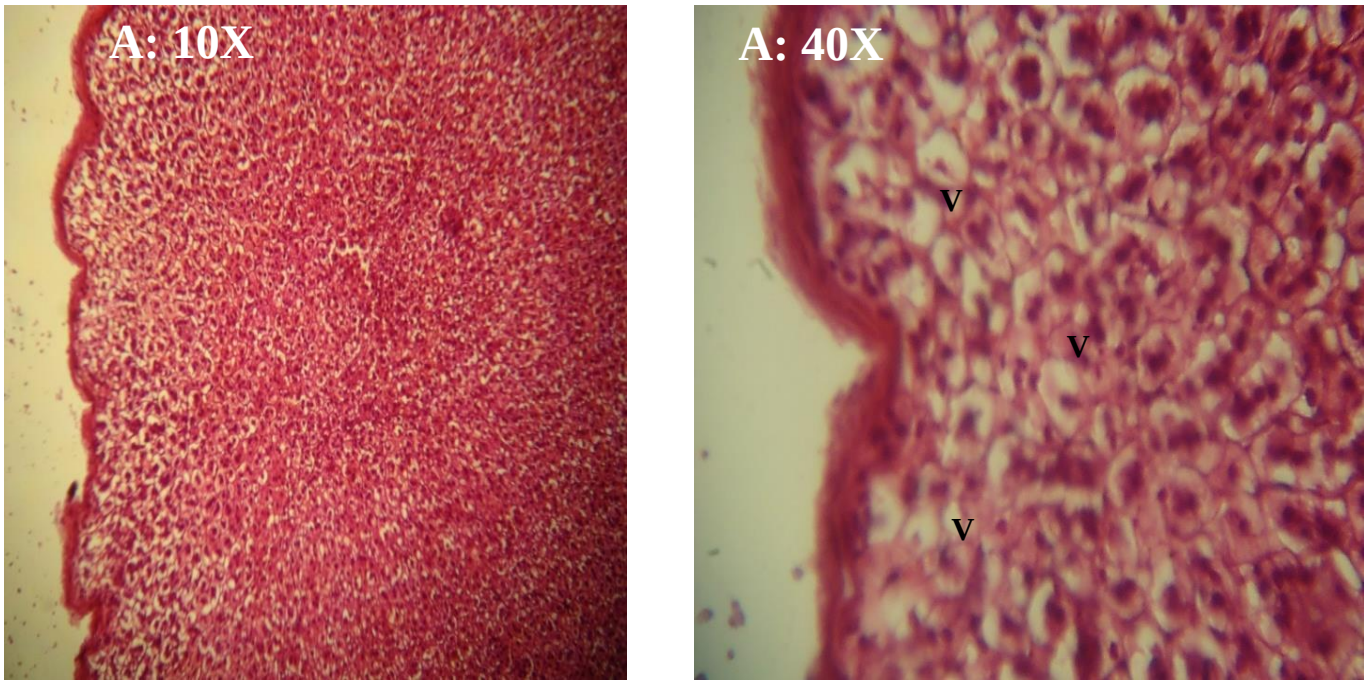

Figure (3): adrenal gland of female rabbit injection(1gm/kg.bw)s/c weekly for 8 week. Show moderated vacuolation of zona glomerulase. Eosin –hematoxylin stain (A: 10X and B: 40X).

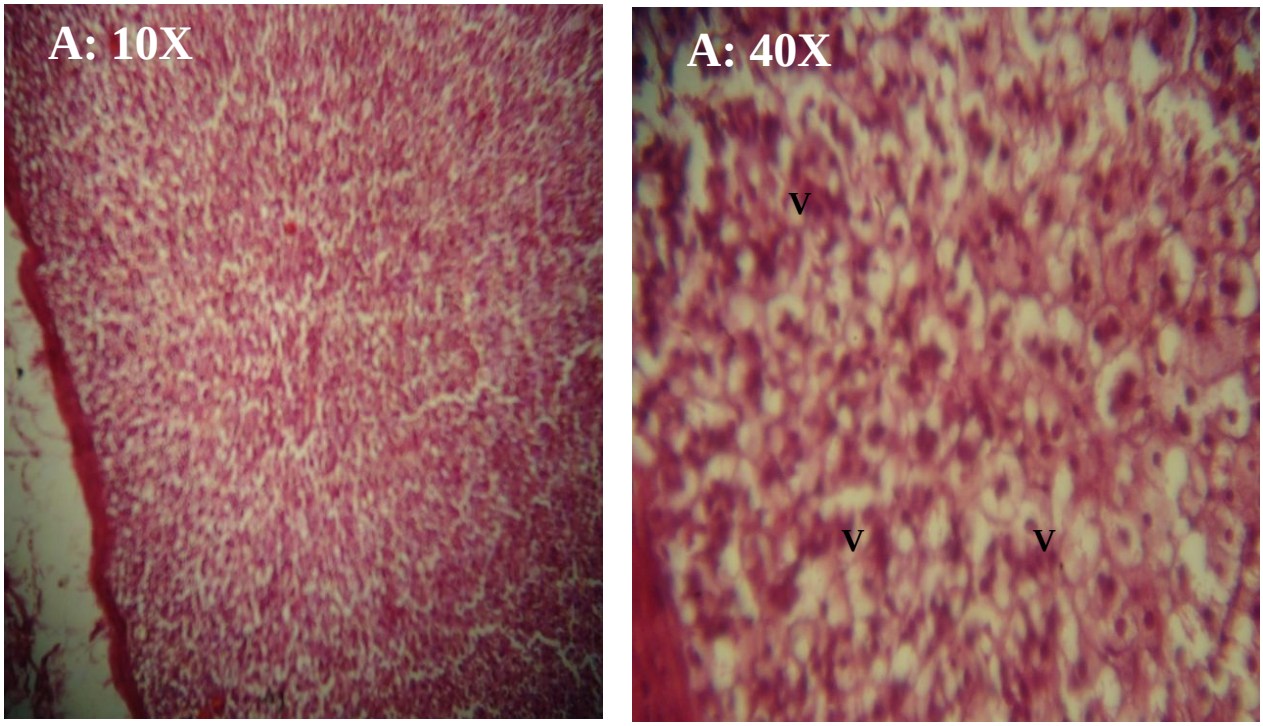

Figure (4): adrenal gland of female rabbit injection (2gm/kg.bw)s/c weekly for 8 week. Show severs vacuolation of zona glomerulose and vaculation of zona faseculata. Eosin – ematoxlyin stain (A: 10X and B: 40X).

Discussion

The result from table 1 showed a significant increase in plasma cortisol levels when injection ivermectin s/c 2mg/kg.bw compared with other dose of ivermectin 1gm/kg.bw or 0.5 gm/kg.bw and control group. This result is Clearfield the effect of ivermectin on adrenal gland histologically and physiologicaly through the study the effect of ivermactin on adrenal biomarker (plasma cortisol) and conducted to the increases significantly in plasma cortisol in group injected with ivermectin at dose 2mg /kg.bw. weekly for 8 weeks compared with control and other doses, whereas the concentration 1gm/kg.bw increased but not reached to the significant. So that come to agreement with Muhammed *et al.* (2022) have reported the negative effects of avermectins like ivermectin, abamectin, doramectin, and eprinomectin on the host animals. These harmful effects arise from avermectins targeting GABA and glutamate-gated chloride channels present both in the parasites and the host animals. The neurotoxicity induced by damaging the brain, which is responsible for production of reproductive hormones; therefore, they indirectly affect the reproductive system of animals (El-shafey *et al.*, 2011 and Labue *et al.,* 2020) Also Ming *et al.* (2013) stated that ivermectin induced pathological changes as neuronal degeneration and necrosis on pigeon brain tissues after sub chronic exposure to different doses of ivermectin at different periods. Similarly, the therapeutic dose of ivermectin in adult rats was found to impair neurochemical and behavioral attitudes injected 1 mg/Kg subcutaneously causes increased serotonergic and dopaminergic in rats activity in association with stress (Parisi *et al.*, 2019). Also GabAllh *et al.* (2017) conducted to injected 0.8 mg/Kg subcutaneously ivermectin for 8 weeks rabbits Meningitis and brain degeneration.

So from earlier study we believe there is a relationship between the effect of ivermectin on neural activity and adrenal gland hormones that resemble with state that is observed a trend towards an increase in serum cortisol levels in chronically infected animals. Serum cortisol is often used in stress and welfare assessments (Orihuela *et al.*, 2009) that is agreement with study In Baladi cows, injected a therapeutic dose (0.2 mg/Kg) of ivermectin one day post-parturition caused 3 months delay in estrous and caused disturbances in the levels of luteinizing hormone, follicle-stimulating hormone, cortisol, estradiol, progesterone, and prolactin (Sadek and Shaheen, 2015), there is a resemble in result with Omshi *et al.* (2018) they found the wide range of use of ivermectin in the treatment of many conditions in animals and humans explains the need of studying its effects on vertebrates especially mammals

Cortisol is a steroid hormone produced by the zona fasciculata of the adrenal cortex. Elevated levels of cortisol in Ivermectin treated rabbit's indication of the stress condition of those animals (El-sawy *et al.*, 2016). Ivermectin is considered a very safe drug when therapeutic doses are respected. However, several toxic effects were reported in sensitive populations or are related to involuntary overdoses. the dose and dosage of ivermectin for animals and humans are changing depending on the clinical case and the type of parasites (Ahmed *et al.*, 2020), while sub-chronic administration of the oral high dose of emamectine benzoate, an avermectin insecticide, was associated only with decreased activity and increasing weakness (Khaldoun-oulabi *et al.*, 2015), ivermectin may produce free radicals and thus results in cytotoxic effect on the parasite. Nitric oxide is involved in various path physiological processes. it acts as free radicals and as host defense mechanisms through cytotoxic effect (Tamarozzi *et al.*, 2011). Since cortisol is a significant hormone that is released as a response to stress (Orihuel *et al.*, 2009; Muehlenbein and Watts, 2010). Cortisol levels in rabbits went up significantly in ivermectin-treated and untreated infested control group.

Histological Changes: In the present study condected to the modifications in plasma cortisol levels markers were confirmed by the histopathological alterations found in the ivermectin treated group including vacuolization in zona fasculata cells when treated with dose 2mg/kg bw. The results correspondence with (Elzoghby *et al.*, 2015; El sawy *et al.*, 2016) in therapeutic and double therapeutic doses of ivermectin treated groups in rats and in rabbits (Gaballh *et al.*, 2017)

According to the literature research, no studies were performed on the histopathological effects of ivermectin on the adrenal gland tissues of animals. Makhlouf *et al.* (2021) found severe alterations of the brain tissues of rabbits when administered a therapeutic dose of ivermectin (degenerative changes in neurons) for 8 weeks and a double therapeutic dose (vesiculation of brain structure) for the same period. In the aforementioned study, it was conducted that the brain lesions were related to the dose and frequency of use of ivermectin results were reported to ivermectin injections alone weekly for 8 weeks of treatment at a dose of 2 mg/kg s/c, resulted in histopathological effects on the liver tissue, including severe swelling and necrosis of some liver cells, hyperplasia of the epithelial cells lining the bile ducts, vascular congestion, and hydropic degeneration of hepatocytes. These findings are consistent with those of another study, which found pathological alterations in the livers cells of ivermectin treated mice (Nashat *et al.*, 2018).

Conclusion:

we concluded the high dose of ivermectin (2mg/kg.bw.) cause a stress effect on adrenal gland of the host, specially zona fasciculate that is led to released cortisol hormone from it.

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